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GAMBEL, P	
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DATE MAILED: 03/07/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on _____ ☑ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-40 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 1-40 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims 0 are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

15. Claims 1-3, 6, 8, 9, 14-16, 21-23, 28-30, 34 and 36 have been amended.

Claims 1-40 are pending and being acted upon.

REJECTIONS WHICH STILL REMAIN AND RESPONSE TO APPLICANT'S ARGUMENTS

16. The previous rejection of claims 1-40 under 35 U.S.C. § 101 is withdrawn.

17. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification. Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

A) Applicant has not disclosed how to use the claimed vaccines and methods to treat prostatic cancer as a therapeutic regimen in humans. There is insufficient evidence of the invention with respect to the in vivo operability of the claimed prostate-specific proteins, peptides or fragments thereof to use applicant's invention.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Concerning vaccines in general, the antigenic or immunogenic nature of a protein or an anti-idiotypic antibody does not necessarily correlate with its ability to confer protective efficacy as a vaccine.

Applicant discloses that prostate cancer continues to be refractory to treatment despite many years of efforts to improve therapy. Similarly, applicant discloses that vaccine development has been slow and no vaccine approved by the FDA for marketing currently exists for any form of cancer. Applicant has not provided any evidence a priori that establishes the efficacy of the instant invention drawn to an antigen (e.g. protein, peptide or fragment thereof) overrepresented in the prostate gland (e.g. PSA, PSMA or PAP) for the treatment of human prostatic cancer. In the instant application where the prostate gland itself is not eliminated, then a further problem could occur by the claimed methods by eliciting prostate specific immunity. The generation of an immune response against self even if it is against tissue-specific antigens could elaborate into an autoimmune response against other antigens (e.g cross-reactive antigens) of the host.

No examples or nexus is provided in the application of prostate-specific antigen-mediated therapy as a therapeutic regimen for human prostate cancer. Therefore it does not appear that the asserted operability of the claimed methods and compositions for inducing antitumor responses in potential or actual prostate tumor-bearing subjects would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

Applicant's arguments have been fully considered but are not found convincing. Applicant states that they do not know whether no satisfactory vaccine has been approved for any form of

cancer by the FDA, as indicated in the last Office action. The examiner is in agreement with applicant's specification on this matter (see page 2, paragraph 1). Applicant also discloses the art-known experience that prostate cancer continues to be refractory to treatment despite many years of effort to improve therapy (page 2, paragraph 1).

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (J. NIH Research, 1995; see entire document, particularly the last paragraph). It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Furthermore, no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (Ezzell; page 48, paragraph 6).

Therefore, applicant's specification is in agreement with the current status of cancer vaccines. While there has been development in cancer immunology, the success of cancer vaccines is still forthcoming and not in currently available form. Applicant has not provided sufficient evidence or nexus a priori that establishes the efficacy of the instant invention for the treatment of human prostatic cancer. In the absence of clear and convincing evidence commensurate in scope with the allegations and claims, applicant's arguments have not been found persuasive. The rejection is maintained.

B) Applicant discloses that the antigens overrepresented on prostate includes any other antigens substantially uniquely present on the prostate gland so that prostate derived tissue can be distinguished from other tissues by virtue of the presence of these antigens (see pages 9-10). There is no evidence relating to overrepresented prostate-specific antigens other than PSA, PSMA and PAP to practice all of the claims vaccine compositions and methods embraced by the claims. The specification has not provided sufficient direction or guidance to one of skill in the art to properly select prostate antigens other than PSA, PSMA that are required to enable the broadly claimed compositions and methods. It appears that undue experimentation would be required of one skilled in the art to practice the broadly claimed

compositions and methods using the teaching of the specification alone.

Applicant's arguments have been fully considered but are not found convincing. Applicant argues the specification provides adequate teaching concerning the appropriateness of any antigen overrepresented on prostate tissue. In the section cited by applicant, the specification is written in terms of an antigen that is "sufficiently higher" in the prostate over other tissues and of an immune response that results in "relatively sparing of other organs and tissues". In consideration with the lack or predictability concerning cancer vaccines, it would be undue experimentation to investigate all the possible variations of possible immunogens that may result in an appropriate prostatic cancer vaccine. Applicant has not enabled a prostatic cancer vaccine based on PSA, PSMA or PAP, which are known prostatic antigens; as indicated above in section A. It would be even less predictable to provide an appropriate prostatic cancer vaccine based on overrepresented prostatic antigens not even known yet. Just because an antigen may be overrepresented, it does not make it a suitable vaccine candidate. Just because an antigen can be made immunogenic, it does not make it a suitable vaccine candidate. In the absence of clear and convincing evidence commensurate in scope with the allegations and claims, applicant's arguments have not been found persuasive. The rejection is maintained.

19. Claims 1-40 stand rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification (see sections 17-18).

21. The previous objection to the specification as failing to provide proper antecedent basis for the claimed subject matter, "neoadjuvant" has been withdrawn due to the deletion of this term.

22. Claims 1-40 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-40 are indefinite in the recitation of "at least one antigen overrepresented in the prostate gland", "peptide", "a fragment thereof", "portion ", "portion thereof", "effective

portion", "portion being less than the complete antigen", "exhibits posttranslation modification different from those of PSA produced in human cells", "immunologically effective portion" and "ingredients which are active to elicit said immune response" because their characteristics are not known. This language is vague and indefinite since it encompasses potentially thousands of different proteins or peptides an it is not apparent from the disclosure which particular proteins or peptides are being referred to. It would require undue experimentation to produce all such possible proteins and peptides without more explicit guidance from the disclosure. No direction or guidance is provided to assist one skilled in the art in the selection of all such possible vaccine derivatives nor is there evidence provided that all such derivatives would be therapeutically effective. It appears that undue experimentation would be required of one skilled in the art to practice the claimed methods and compositions in providing effective vaccines for prostatic cancer using the teaching of the specification alone.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

Applicant's arguments have been fully considered but are not found convincing. Applicant argues that it is not clear what is the objection to these terms. Applicant has amended the claims to include such terms as "immunologically effective portion" and "ingredients which are active to elicit said immune response" to overcome the rejection. Applicant argues that toxicity parameters are provided, that a peptide is simply represents a subset of the antigen and that the other terms are defined in the specification.

Applicant is reminded that the invention is drawn to eliciting an effective prostatic tumor immune response. As pointed out in section 18 A above, the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (J. NIH Research, 1995; see entire document, particularly the last paragraph). It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Furthermore, no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose

tumors have been surgically removed or killed by radiation or chemotherapy (Ezzell; page 48, paragraph 6).

No clear guidance as to the metes and bounds of the various terms set forth above has been provided other than that they should be immunogenic. However, applicant is claiming a universe of antigens yet it is unclear whether any overrepresented prostatic antigen would provide the appropriate vaccine preparation. In turn, it is not clear whether any portion of any of these overrepresented prostatic antigens would stimulate an effective vaccination. It is clear that the art recognizes that a single peptide is not likely to provide an effective vaccine, as disclosed by Ezzell. Again, just because an antigen (or portion thereof) is immunogenic, this does not make it effective as a vaccine. There are no adequate working examples to indicate that any immunogenic portion of any overrepresented prostate antigen or portion thereof would provide an effective vaccine. Applicant's arguments have not been found persuasive and the rejection is maintained including the amended phrases.

23. The previous rejection of claims 1-40 under 35 U.S.C. § 112, second paragraph, have been withdrawn due to the amended or canceled claims.

24. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

25. Claims 1-40 stand rejected under 35 U.S.C. § 103 as being unpatentable over Chu et al. (1449, #3; U.S. Patent No. 4,446,122) in view of Dai et al. (FASEB J., 1988), Deguchi et al. (Cancer Research, 1986), Brown et al. (U.S. Patent No. 5,262,177) and Alving (J. Immunol. Methods, 1991) and the art-known vaccine and recombinant technology acknowledged throughout the specification. Claims 1-40 are drawn to vaccine compositions and methods that employ prostate-specific antigens in the treatment of prostatic cancer.

From a reading of the specification, the alleged novelty of the instant application appears to rest with the statement that there has been no report of the use of antigen protein or an antiidiotypic antibody bearing the internal image of the prostate antigen as a vaccine for prostate cancer (see page 2, lines 19-23). Applicant discloses that the prostate antigens, surgical treatment associated with prostate cancer, adjuvant formulations and recombinant technology were all known at the time the invention was made; therefore the claimed limitations of these aspects were known or obvious at the time the invention was made. Similarly, Brown et al. teach the art-known recombinant viruses in the derivation of vaccines (including adjuvants) based on tumor-associated antigens. Also, Alving teach the art-known use of liposomes as carriers of antigens and adjuvants in vaccine technology.

Chu et al. teach the characterization of the PSA antigen (see entire document), its use in immune-specific chemotherapy (column 6, paragraph 1) and its use preparing diagnostic antibodies and vaccine preparation (see column 7, paragraph 3). Dai et al. teach the generation and characterization of anti-idiotypic antibodies for prostate tumors (see Abstract). Deguchi et al. teach the use of PAP-specific antibody conjugates for the treatment of prostate tumor (see entire document). Therefore the prior art did recognize the use of prostate-specific antigens in the derivation of therapeutic regimens to treat prostate cancer.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of prostate-specific antigens as vaccines in the treatment of human prostate cancer. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have been fully considered but are not found convincing. Applicant essentially argues that the combination of references do not suggest the use of antigens which are uniquely represented on host tissue in antitumor vaccines. However, Dai et al. clearly teach the value of anti-idiotypic antibodies to modulate the immune response to prostate tumor (see last line of the Abstract). Deguichi et al. clearly teach targeting PAP as a therapeutic modality, an overrepresented prostate antigen that is targeted by the instant invention. As indicated above, Chu et al. clearly teach the PSA antigen as a target of immune-specific chemotherapy. Therefore, the combined references do teach the prostatic host tissues antigens as targets for treatment and Dai et al. teach prostatic antitumor vaccines. In combination with the art-known teachings such as Brown, the making of tumor-associated antigen vaccines was known. It would have been obvious at the time the invention was made to target tumor-associated antigens through various modalities including immunotoxins and vaccines. Applicant's argument concerning the extrapolation from animals models to human efficacy is not convincing in view that no working examples have been provided by applicant. Therefore, applicant's arguments have not been found persuasive and the rejection is maintained.

26. Claims 1-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of copending application Serial No. 08/288,057. Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are drawn to essentially the same or similar compositions and methods drawn to vaccination with the same overrepresented prostatic antigens.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

27. No claim is allowed.

28. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

29. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. David Lacey can be reached on (703) 308-3535. The fax phone number for Group 180 is (703) 305-3014 or (703) 308-4227. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
March 3, 1995

DAVID L LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
3/6/95